Caffeine Modulates Attention Network Function

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14. ABSTRACT

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Abstract

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Caffeine Modulates Attention Network Function

Introduction

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychoactive stimulant in the world, found naturally in many foods and beverages, and often cited for its positive effects on vigilance and mental alertness (for reviews, see IOM, 2001; Koelega, 1993; Lieberman, 1992, 2001; Smith, 2002; Snel, Lorist, & Tieges, 2004; Spiller, 1997). Improvements in these processes have been commonly attributed to caffeine's antagonistic role at adenosine A_1 and A_{2A} receptors in dopamine-rich brain areas, ultimately stimulating dopaminergic activity and resulting in increased wakefulness and pronounced motor activity (i.e., Garrett & Griffiths, 1997; Popoli, Reggio, Pezzola, Fuxe, & Ferré, 1998; Solinas, Ferré, You, Karcz-Kubicha, Popoli, & Goldberg, 2002). Indeed, many studies have demonstrated that caffeine reduces response times and error rates in tasks such as simple reaction time (Wesensten, Killgore, & Balkin, 2005), choice reaction time (Kenemans & Lorist, 1995; Lieberman, Tharion, Shukitt-Hale, Speckman, & Tulley, 2002), and visual vigilance (Fine, Kobrick, Lieberman, Marlowe, Riley, & Tharion, 1994; Lieberman et al., 2002). Further work suggests that caffeine may have positive influences on relatively higher-order processes such as visual selective attention (Lorist & Snel, 1997; Lorist, Snel, Kok, & Mulder, 1996; Kenemans, Wieleman, Zeegers, & Verbaten, 1999; Ruijter, De Ruiter, & Snel, 2000), task switching (Tieges, Snel, Kok, Plat, & Ridderinkhof, 2007; Tieges, Snel, Kok, Wijnen, Lorist, & Ridderinkhof, 2006), conflict monitoring (Tieges, Ridderinkhof, Snel, & Kok, 2004), and response inhibition (Barry, Johnstone, Clarke, Rushby, Brown, & McKenzie, 2007).

Other work, however, suggests that whereas caffeine may improve overall processing speed on tasks requiring higher-order function, these improvements cannot be attributed to specific effects on response inhibition or selective visual attention (Kenemans & Verbaten, 1998; Lorist & Snel, 1997; Tieges, Snel, Kok, & Ridderinkhof, 2009). To further elucidate the locus of caffeine effects on lower- versus higher-level visual attention, we examined whether caffeine differentially affects the function of three visual attention networks in a dose-response paradigm. Specifically, we used the Attention Network Test (Fan, McCandliss, Sommer, Raz, & Posner, 2002), which is a modified flanker task that allows examination of the relative functioning of alerting, orienting and executive control networks (i.e., Posner, 1990) in a single unitary visual attention task. Our intention was to examine whether caffeine consumption ranging from 0 mg to 400 mg differentially affects lower- versus higher-order attention network functioning, and how these effects might be modulated by dose.

Caffeine: Psychopharmacology & Physiology

Caffeine is a psychoactive stimulant that is abundantly available in both natural (e.g., coffee, tea, chocolate) and supplemented (e.g., soft drinks, energy bars) food and beverages, as well as over-the-counter remedies for migraines, colds, and fatigue (Gilbert, Marshman, Schwieder, & Berg, 1976; James, 1991). Some studies estimate that over 80% of US adults and children habitually consume moderate daily amounts of caffeine (estimates range from 193-280 mg/day average; Barone & Roberts, 1996; Frary, Johnson, & Wang, 2005), likely due to its properties as a mild psychostimulant (Childs & de Wit, 2006). Peak plasma concentrations of caffeine occur in as few as 15 minutes and on average approximately 45 minutes after ingestion (Arnaud, 1987; Smith, 2002). A number of studies suggest that the most behaviorally-relevant role of caffeine is in blocking the inhibitory properties of endogenous adenosine (particularly at

A_1 and A_{2A} receptors), resulting in increased dopamine, norepinephrine and glutamate release (e.g., Ferré, Fredholm, Morelli, Popoli, & Fuxe, 1997; Fredholm, Arslan, Johansson, Kull, & Svenningsson, 1997; Smits, Boekema, Abreu, Thien, & van't Laar, 1987). The effects of caffeine on physiological functions are thought to result from interactions with both adenosine and phosphodiesterase, resulting in cardiostimulatory and antiasthmatic actions (Davis, Zhao, Stock, Mehl, Buggy, & Hand, 2003; IOM, 2001). The result of higher dopamine and glutamate concentrations, coupled with phosphodiesterase inhibition, is a net increase in central nervous system and cardiovascular activity. In addition to affecting cognitive performance, caffeine increases perception of alertness and wakefulness (Leathwood & Pollet, 1982; Rusted, 1999) and sometimes anxiety (particularly at high doses; Lieberman, 1992; Loke, Hinrichs, & Ghoneim, 1985; Sicard, Perault, Enslen, Chauffard, Vandel, & Tachon, 1996).

Caffeine: Behavior and Cognition

Presumably as a direct result of altered CNS activity, caffeine appears to result in performance improvements on a variety of basic psychomotor tasks. For instance, performance on simple and choice reaction time tasks is faster and accuracy improves as a function of increasing doses (Kenemans & Lorist, 1995; Lieberman et al., 1987; Lieberman, Tharion, Shukitt-Hale, Speckman, & Tulley, 2002; Wesensten, Killgore, & Balkin, 2005); other work suggests that these advantages diminish with very high doses of caffeine (e.g., 600 mg; Roache & Griffiths, 1987). Extended vigilance is also generally improved following caffeine consumption (Lieberman et al., 1987; Frewer & Lader, 1991; Mitchell & Redman, 1992). More recently, research has begun to examine the mechanisms responsible for these performance advantages. Lorist and Snel (1997) found that caffeine reduces stimulus evaluation times as reflected in the timing of electroencephalography (EEG) components (see also Lorist, Snel, Kok,

& Mulder, 1996). Further work suggests that caffeine can shorten motor readiness potentials as measured by EEG during ergometer exercise (Barthel, Mechau, Wher, Schnittker, Liesen, & Weiss, 2001). Basic psychomotor tasks thus appear to be improved by more efficient stimulus feature analysis (i.e., Treisman & Gelade, 1980) and shorter-duration readiness potentials, leading to decreased overall response times; these effects also appear to be generally greater at higher doses.

More recently, research has identified some higher-order cognitive processes that caffeine appears to affect. In general, higher-order processes are those considered to be involved in the active monitoring, guidance, and coordination of behavior (Miller & Cohen, 2001). Tieges and colleagues have recently demonstrated that caffeine can reduce response time costs during task switching (Tieges et al., 2006, 2007), and strengthen action monitoring (Tieges et al., 2004). Another component of higher-order cognitive function is inhibitory control, generally defined as the ability to inhibit inappropriate impulses and actions, and reduce the influence of interfering (and often action-incompatible) information (Shallice & Burgess, 1993). Work investigating inhibitory control suggests that caffeine can reduce interference costs during selective visual attention tasks (Lorist, Snel, Kok, & Mulder, 1994, 1996) and the Stroop color-word task (Hasenfratz & Battig, 1992; Kenemans, Wieleman, Zeegers, Verbaten, 1999; but for contradictory results, see Foreman, Barraclough, Moore, Mehta, & Madon, 1989). Other work, however, suggests that caffeine (in a 3 mg/kg dose) does not significantly reduce interference on a variety of inhibitory tasks, including a cued go/no-go paradigm, a stop-signal task, and a flanker task (Kenemans & Verbaten, 1998; Tieges et al., 2009). Thus, results are mixed with regard to caffeine's effects on higher-order control processes.

Several methodological characteristics might account for such contradictory results. First, as noted by Tieges and colleagues (2009), the caffeine doses used in previous work may not have been large enough to elicit effects on inhibitory control (p. 325). Indeed a dose approximating 200 mg may not be sufficiently high to produce changes in individuals who habitually drink 2-4 cups of coffee per day (i.e., 170-340 mg) (i.e., Kenemans & Verbaten, 1998; Tieges et al., 2009). Further, habitual coffee drinkers may be affected by both withdrawal effects and caffeine response (see James, 1994; Juliano & Griffith, 2004), and the use of a predominantly female sample (89% female; Tieges et al., 2009) in the flanker task may limit the chances of finding caffeine effects on cognitive performance (i.e., females may be less prone to the effects of caffeine on cognitive performance; Gupta & Gupta, 1999).

As noted by Tieges and colleagues (2009), there is convincing evidence, however, to expect that caffeine might modulate the inhibitory control of attention, particularly on visual selective attention tasks. First, some research has demonstrated that caffeine improves conflict resolution in the classic Stroop task, which involves resolving a visual conflict between a word name and its color (i.e., Hasenfratz & Battig, 1992; Kenemans et al., 1999). Second, meta-analyses of brain activation during the Stroop task reveal a network including the anterior cingulate cortex and a number of regions in the prefrontal cortex (Bush, Luu, & Posner, 2000; Bush, Whalen, Rosen, Jenike, McInerney, & Rauch, 1998); similar results are found with performance monitoring and conflict resolution during flanker tasks, most often implicating the anterior cingulate cortex (ACC; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Casey, Thomas, Welsh, Badgaiyan, Eccard, Jennings, & Crone, 2000; Fan, Flobaum, McCandliss, Thomas, & Posner, 2003; MacDonald, Cohen, Stenger, & Carter, 2000). Given fMRI evidence that the ACC is up-regulated by caffeine, one might expect facilitation of conflict resolution

either in the form of reduced response times or reduced error rates during flanker tasks (Koppelstaetter, Poeppel, Siedentopf, Ischebeck, Verius, Haala, Mottaghy, Rhomberg, Golaszewski, Gotwald, Lorenz, Kolvitsch, Felber, & Krause, 2008).

In support of this position, it should be noted that the ACC has dense dopaminergic innervation (Lumme, Aalto, Ilonen, Nagren, & Hietala, 2007) and dopamine binding in this region drives executive function (Ko, Ptito, Monchi, Cho, Van Eimeren, Pellecchia, Ballanger, Rusjan, Houle, & Strafella, 2009). These findings suggest a potential role of increased dopamine availability as a result of caffeine consumption in brain regions mediating executive control, and that the result of such a process may be enhanced monitoring and conflict resolution.

The Present Study

To further examine the locus of caffeine's effects on lower- and higher-order visual attention, we conducted a double-blind, within-participant repeated-measures design with four levels of our Treatment variable (0 mg, 100 mg, 200 mg, 400 mg caffeine). We assessed how caffeine affects visual attention in non-habitual consumers by using the Attention Network Test (ANT; Fan et al., 2002). The ANT simultaneously tests the individual performance of the three networks in Posner's (1990) attention model by combining cued reaction time (Posner, 1980) and flanker tasks (Eriksen & Eriksen, 1974). Posner's three attention networks involve alerting, orienting, and executive attention.

The *alerting* network allows an individual to achieve and maintain a state of alertness during task performance by using predictive cues about trial onset. Alerting cues have been found to activate the thalamus and right and left frontal and parietal brain regions, similar to results found with vigilance and sustained attention tasks (Coull, Frith, Frackowiak, & Grasby,

1996; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Marrocco & Davidson, 1998; Posner & Peterson, 1990). Given the dense dopaminergic innervation of the human thalamus and prefrontal cortex (Sánchez-González, García-Cabezas, Rico, & Cavada, 2005; García-Cabezas, Rico, Sánchez-González, & Cavada, 2007; Sawaguchi & Goldman-Rakic, 1991, 1994; Williams & Goldman-Rakic, 1995), and that caffeine is generally found to improve simple reaction times on several simple psychomotor tasks, we expected similar effects in a positive dose-response relationship. Specifically, we expect that the advantage of cued versus non-cued trials in the ANT would increase as a function of higher caffeine dose.

The *orienting* network allows an individual to selectively attend to regions of space by directing attention to cued areas. Orienting attention (either covertly or overtly) towards particular regions of space has been found to activate the superior parietal lobe (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Fan et al., 2005). No work to date has specifically investigated caffeine's effects on the orienting function of visual attention. However, we hypothesize that given work demonstrating relatively sparse dopaminergic innervations of the parietal lobes, the orienting network may not be specifically affected by caffeine consumption (i.e., Lidow, Goldman-Rakic, Rakic, & Innis, 1989; Tassin, Bockaert, Blanc, Stinus, Thierry, Lavielle, Prémont, & Glowinski, 1978). As such, we do not expect that caffeine will differentially affect people's ability to take advantage of spatial cues that orient them towards particular areas of space.

The *executive attention* network allows an individual to resolve a conflict among potential responses to a presented stimulus. As with the Stroop task, resolving conflict during the flanker task generally activates the anterior cingulate and lateral prefrontal cortices (Botvinick et al., 2001; Bush et al., 2000; Casey et al., 2000; Fan et al., 2005; MacDonald et al., 2000). Given

the dense dopaminergic innervation of these areas (as reviewed above), and that caffeine could reasonably be expected to enhance the executive control of attention, we expect caffeine may modulate executive control by improving conflict resolution during flanker tasks, particularly with higher doses of caffeine. This hypothesis does not run specifically counter to the results of Tieges and colleagues (2009); indeed it is possible that lower doses may not produce significant effects on conflict resolution. We do expect, however, that a higher dose (i.e., 400 mg) may enhance performance. Specifically, higher doses of caffeine may diminish the cost of presenting action-incompatible relative to action-compatible flankers in the ANT.

Method

Participants

Thirty-six Tufts University undergraduate students (16 male, 20 female; mean age 19.08; mean BMI 23.15) participated for monetary compensation ($10 USD/hr). All participants reported being low caffeine consumers (M = 42.5 mg/day), non-smokers, in good health, not using prescription medication other than oral contraceptives, and not using nicotine in any form. Written informed consent was obtained, and all procedures were jointly approved by the Tufts University Institutional Review Board and the Human Use Review Committee of the U.S. Army Research Institute for Environmental Medicine.

Design

We used a double-blind, repeated-measures design with four levels of our independent variable, Treatment (0 mg, 100 mg, 200 mg, 400 mg caffeine). Our highest dose was chosen given its similarity to caffeine levels found in the 20 oz coffee at a major franchise coffee house (i.e., 420 mg). Treatment order was counterbalanced across participants using a Latin square. Each

treatment dose was administered in an identical color, size, weight and shape capsule. Placebo capsules were filled with physiologically-inert microcrystalline cellulose powder, which was also used as filler material in the two lower-dose caffeine capsules. The caffeine was 99.8% pure anhydrous USP-grade powder. Participants were tested during morning sessions following a 12-hour fast during which they were only to consume water. A 12-hour fast is thought to be a sufficient wash-out period to attenuate the effects of earlier caffeine consumption, particularly given that we only tested low consumers, and that the mean plasma and elimination half-lives of caffeine are both approximately 5 hours in healthy individuals (Culm-Merdek, von Moltke, Harmatz, & Greenblatt, 2005; IOM, 2001; Statland & Demas, 1980). To encourage fasting compliance we collected saliva samples upon arrival for each test session (not further analyzed herein; see also Tieges et al., 2009). Participants were further instructed not to use any over-the-counter medications or herbal supplements for 24 hours prior to testing.

Materials

Self-Reported Mood State. Participants completed the Brief Mood Introspection Scale (BMIS; Mayer & Gaschke, 1988) upon arrival to each test session and immediately prior to ANT administration.

Attention Network Test. The ANT involves viewing a sequence of visual cues and arrows and responding to the direction of a central arrow. A cue can alert an individual that a trial is about to be presented only, or it can also orient the individual to a particular region of space (above or below fixation). A central target arrow is then presented within an array of congruent (same facing direction), incongruent (opposite facing direction), or neutral (no facing direction) flankers. Response time and accuracy are measured when the participant responds to the

direction (left or right) of the central arrow. Three primary indicators of attentional function are calculated from the ANT data; first, one can compute the extent to which cues are *alerting* the participant of an upcoming trial, relative to when no cue is provided (i.e., alerting network function). Second, one can compute the extent to which spatially-determinate cues are *orienting* the participant towards a particular region of the screen, relative to spatially-indeterminant cues (i.e., orienting network function). Finally, one can compute the extent to which incongruent relative to congruent or neutral flankers interfere with the determination of and response to a central arrow's facing direction (i.e., *executive control* network function). Behavioral, neuropsychological, and neuro-imaging evidence support the validity and reliability of the ANT as well as the notion of three independent attentional networks (i.e., Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Fan, Fossella, Sommer, Wu, & Posner, 2003; Neuhaus, Koehler, Opgen-Rhein, Urbanek, Hahn, & Dettling, 2007; Posner & Rothbart, 2005).

The ANT presents an easily-implemented and time-efficient method for measuring the separable contributions of the three attentional networks toward task performance. The test involves three blocks of 96 trials (total of 288 trials) presented in random order. Each block presents two trials for each of the four cue conditions (none, center, double, spatial), two target locations (top, bottom), two target directions (left, right), and three flanker conditions (neutral, congruent, incongruent). On each trial, the participants identify and respond to the center arrow's facing direction (left or right). For a more complete description of the task and its parameters, refer to (Fan et al., 2002).

Procedure

Participants completed six sessions: one intake session, one practice session during which participants were told to consume their normal caffeine amounts, and four test sessions corresponding to each Treatment level. During the intake session, participants were fully screened and completed the informed consent. During the practice session, participants completed the BMIS, provided 6 ml saliva samples (not further analyzed here), and then practiced the complete ANT; they received full instructions on how to perform the task and had the opportunity to ask questions during two 3-minute breaks (one following each block of 96 trials). Participants were told to respond to the center arrow's facing direction as quickly and accurately as possible; they were also told that on some trials they would receive an indication of when the trial was about to begin and/or where the trial would appear.

The practice and test sessions always took place in the morning at consistent times within participants, and each session was separated by at least three days. Test sessions were similar to the practice day with the exception of capsule consumption and a digestion period. During test sessions, participants completed the BMIS upon arrival, provided 6 ml saliva samples, and then consumed their assigned treatment capsule along with a cup of water. They then took a thirty-minute break; we chose this period of time in consideration of research showing that caffeine peak plasma concentrations vary widely and occur between 15 and 120 minutes after consumption (Arnaud, 1987; IOM, 2001). Following the break, participants again completed the BMIS and then began the ANT. Participants received two 3-minute breaks during the ANT, and were tested in groups of up to 5 participants (each with an isolated workstation).

Results

Self-Reported Mood State. Table 1 details adjective ratings as a function of Treatment. Repeated-measures analyses of variance (ANOVA) on adjective ratings following caffeine consumption confirmed the effectiveness of our Treatment manipulation. Overall, there were significant increases in participants' ratings of how *Lively, Peppy,* and *Jittery* they felt as a function of Treatment level; conversely, there were also significant decreases in participants' ratings of how *Drowsy, Tired,* and *Calm* they felt as a function of Treatment level. For adjectives with significant ANOVA results, Table 1 also lists Bonferroni-corrected ($\alpha = .017$) t-test results, comparing each treatment level to 0mg placebo.

Attention Network Test

Replication of Original ANT Results. First, we conducted two 4 (Cue Type: none, center, double, spatial) × 3 (Flanker Type: neutral, congruent, incongruent) repeated-measures ANOVAs in the 0 mg condition, one on RT and one on accuracy data. These tests were designed to confirm replication of the original ANT results (i.e., Fan et al., 2002). Response time data replicated earlier results, with a main effect of Cue Type, $F(3, 147) = 36.62$, $p < .01$, and Flanker Type, $F(2, 98) = 19.75$, $p < .01$, and an interaction between these two variables, $F(6, 294) = 2.54$, $p < .05$. Overall, incongruent flankers increased response times relative to congruent or neutral flankers, and this effect was greatest when participants were given spatially indeterminate (center or double) relative to spatial determinate (top/bottom) cues. Accuracy data further replicated earlier results, with a marginal main effect of Flanker Type, $F(2, 66) = 2.35$, $p < .10$, suggesting that incongruent flankers showed lower accuracy relative to neutral and congruent flankers.

Omnibus Assessment of Treatment Effects. Second, we conducted two omnibus 4 (Cue Type: none, center, double, spatial) × 3 (Flanker Type: neutral, congruent, incongruent) × 4 (Treatment: 0 mg, 100 mg, 200 mg, 400 mg) repeated-measures ANOVAs, one on RT and one on accuracy data. These analyses were designed to test whether Treatment level differentially affected performance on the ANT test. Response time data analysis showed a main effect of Treatment, $F(3, 147) = 17.7$, $p < .01$ (overall RTs: 0mg, $M = 523.43$, $SE = 16.28$; 100mg, $M = 500.82$, $SE = 13.41$; 200mg, $M = 496.38$, $SE = 14.23$; 400mg, $M = 489.97$, $SE = 14.32$), and that Treatment interacted with Cue Type, $F(9, 441) = 2.29$, $p < .05$, and marginally with Flanker Type, $F(6, 294) = 2.05$, $p < .10$. Accuracy data did not reveal any main or interactive effects of Treatment and thus will not be further analyzed.

Treatment Effects on Attention Networks. Third, we calculated difference scores for each of the three attention networks: alerting, orienting, and executive control. Difference scores allow for the independent assessment of each attention network (i.e., Fan et al., 2002; Fan et al., 2005; Redick & Engle, 2006), and are calculated as follows. The alerting difference score was calculated by subtracting average double-cue RTs from the no-cue RTs; higher difference scores thus indicate more efficient functioning of the alerting system. The orienting difference score was calculated by subtracting average spatial cue RTs from center cue RTs; higher difference scores thus indicate more efficient functioning of the orienting system. Finally, a conflict difference score was calculated by subtracting average congruent flanker RTs (across all cue types) from incongruent flanker RTs; lower difference scores thus indicate more efficient functioning of the conflict (executive control) system. Figure 1 depicts difference scores for each of the three attention networks and four Treatment levels.

We then conducted three single-factor repeated-measures ANOVAs with four levels of the Treatment variable (0 mg, 100 mg, 200 mg, 400 mg), one for each attention network difference score (see Figure 1). Analysis of alerting difference scores demonstrated an effect of Treatment, $F(3, 105) = 2.99$, $p < .05$. Planned comparisons revealed lower alerting difference scores in the 0 mg condition relative to both the 200 mg, $t(35) = 3.35$, $p < .01$, and 400 mg, $t(35) = 2.58$, $p < .02$, conditions (all other comparisons $p > .05$). In general, higher doses of caffeine led to enhanced alerting system function; this effect, however, appears to asymptote at 200 mg. Analysis of orienting difference scores demonstrated a marginal effect of Treatment, $F(3, 105) = 2.5$, $p = .06$. Planned comparisons revealed higher orienting difference scores in the 0 mg condition relative to the 400 mg condition, $t(35) = 2.3$, $p < .05$ (all other comparisons $p > .05$). Interestingly, higher doses of caffeine led to diminished orienting system function, only becoming significant at the highest dose. Analysis of the conflict difference scores also demonstrated an effect of Treatment, $F(3, 105) = 3.30$, $p < .05$. Planned comparisons revealed higher conflict difference scores in the 0 mg condition relative to both the 200 mg, $t(35) = 2.28$, $p < .05$, and 400 mg, $t(35) = 2.32$, $p < .05$, conditions (all other comparisons $p > .05$). In general, higher doses of caffeine led to enhanced executive control of attention; as with alerting, however, this effect appears to asymptote at 200 mg.

Testing for Withdrawal Effects. To confirm that our results cannot be attributed to withdrawal effects, we conducted three *t*-tests comparing the practice day to the 0 mg day, one for each of the three attention network difference scores. Recall that participants were instructed to consume normal daily caffeine amounts on the practice day. No differences were revealed when comparing alerting scores, $t(33) = .31$, $p > .05$, orienting scores, $t(33) = .06$, $p > .05$, or executive control scores, $t(33) = .11$, $p > .05$, across the two sessions.

Discussion

The present study examined the effect of four caffeine doses on lower- and higher-level visual attention networks as defined by Posner's (1990) model and assessed with the attention network test. This test independently assesses the function of the alerting, orienting, and executive control networks. Caffeine differentially modulated visual attention as a function of both treatment dose and network function assessed. In general, higher doses of caffeine improve performance of the alerting and executive control networks, but slightly diminish orienting network performance. Below we outline our results and discuss implications as a function of attention network.

Alerting Network

The alerting network is theorized to be responsible for maintaining an alert state throughout task performance (Fan et al., 2002; Fan et al., 2005; Posner, 1990, 2004). The ANT assesses alerting network function by evaluating whether participants can take advantage of cues that alert them to trial onset. The extent to which response times are speeded by such cues is a reliable indication of alerting network function (Fan et al., 2002; Fan et al., 2005). Consistent with caffeine's well-known effects on lower-level visual attention tasks, we found that 200 mg and 400 mg of caffeine can improve participants' ability to take advantage of alerting cues. This result adds to a growing body of literature demonstrating that caffeine can have positive influences on basic psychomotor tasks (Frewer & Lader, 1991; Kenemans & Lorist, 1995; Lieberman et al., 1987; Lieberman, Tharion, Shukitt-Hale, Speckman, & Tulley, 2002; Mitchell & Redman, 1992; Wesensten, Killgore, & Balkin, 2005).

The alerting network (as assessed by the ANT) was recently found to recruit a distributed network of brain regions, primarily the thalamus and bilateral frontal and parietal brain regions (Fan et al., 2005). Given the dense dopaminergic innervation of the human thalamus and prefrontal cortex (Sánchez-González, García-Cabezas, Rico, & Cavada, 2005; García-Cabezas, Rico, Sánchez-González, & Cavada, 2007; Sawaguchi & Goldman-Rakic, 1991, 1994; Williams & Goldman-Rakic, 1995), and that caffeine is generally thought to up-regulate dopaminergic availability (Ferré et al., 1997; Fredholm et al., 1997; Smits et al., 1987), the present results are consistent with the theorized effects of caffeine on CNS function. Further, we show that in non-habitual low caffeine consumers, the effects of 100 mg of caffeine on alerting function are negligible. Only with higher doses (200 mg or 400 mg) were we able to identify reliable effects of caffeine on this lower-level attention network.

Orienting Network

Aptly named, the orienting network is theorized to be responsible for allowing individuals to selectively attend to particular regions of space and ultimately speed selecting and responding to visual stimuli (Fan et al., 2002; Fan et al., 2005; Posner, 1990, 2004). The ANT assesses orienting network function by determining whether participants can take advantage of cues that orient them towards upper and lower region of the screen, allowing them to better-prepare for upcoming trial location. The extent to which response times are speeded by upper or lower cues (relative to spatially-indeterminate cues) is a reliable indication of orienting network function (Fan et al., 2002; Fan et al., 2005). Until now, no research has examined how caffeine specifically affects the orienting network of visual attention. Presently, we found some evidence that high doses (400 mg) of caffeine can produce decrements in orienting network function, with

participants less able to take advantage of spatially-determinate cues to focus visual attention in particular screen areas.

As noted in our hypotheses, we expected that caffeine would have little to no effect on orienting network function; this hypothesis was based on research demonstrating that orienting is primarily the locus of the parietal lobes (i.e., Corbetta et al., 2000; Fan et al., 2005), and some work showing rather sparse dopaminergic innervation of this brain region in humans and other animals (Lidow et al., 1989; Tassin et al., 1978). It is unclear why caffeine showed a negative influence on orienting function. Some recent work in our laboratory, however, has demonstrated that high doses of caffeine (i.e., 400 mg) lead individuals to focus more on global rather than local elements of visual scenes (Mahoney, Brunyé, Lieberman, Shirer, Augustyn, & Taylor, 2009); similar global focus effects have been shown at high levels of arousal (Brunyé, Mahoney, Augustyn, & Taylor, 2009; Corson & Verrier, 2007; Pesce, Tessitore, Casella, Pirritano, & Capranica, 2007). Given these results, one might expect that orienting visual attention to relatively local regions of space might be impaired at higher doses of caffeine. It is difficult to reconcile this explanation, however, with the executive control results; that is, if participants show relatively global visual attention biases at 400 mg of caffeine, they might also show difficulty inhibiting the influence of incompatible flankers (the present results show the opposite effect).

An alternative explanation for the reduced orienting scores is the possibility that such a pattern may indicate *improvement* in orienting function rather than a decrement, per se. This possibility has been put forth by Fan and Posner (2004) as well as Wang and Fan (2007), who suggest that at high levels of intrinsic orienting function, individuals may take less advantage of (or are less dependent upon) orienting cues. In light of the present results this rationale would

suggest that caffeine may improve the intrinsic efficiency of the orienting network, which may appear (in a numerical sense) as reduced orienting scores on the ANT. This is an intriguing possibility. Given that the present effect on orienting function was only marginally significant, future research should attempt to replicate this effect and, if persistent, seek to identify its origins.

Executive Control Network

The executive control network is theorized to be responsible for allowing individuals to inhibit action-incompatible visual information (i.e., conflict resolution), in this case the effects of incongruent relative to congruent or neutral flanker arrows (Fan et al., 2002; Fan et al., 2005; Posner, 1990, 2004). The ANT assesses executive control by evaluating whether participants can inhibit the effects of opposite-facing flankers while responding only to the direction of the center arrow, relative to trials when the flankers were congruent (and in some cases neutral; Fan et al., 2002). The extent to which performance is slowed by incongruent flankers demonstrates the inefficiency of executive control (Fan et al., 2002; Fan et al., 2005). Until now, results have been mixed with regard to the effects of caffeine on tasks demanding selective visual attention; indeed some have demonstrated improvement on these tasks (Lorist et al., 1994, 1996) and others have identified no reliable effects (Kenemans & Verbaten, 1998; Tieges et al., 2009). We show that low caffeine consumers exhibit dose-dependent increases in executive control function at doses exceeding those typically used in previous studies (i.e., 200 mg, 400 mg). The present findings underscore the importance of investigating caffeine effects on highly sensitive and unified tasks in a dose-response manner, particularly at doses exceeding an individual's ordinary consumption levels. We do note, however, that these doses are similar to those found in commonly-consumed

beverages. For instance, 20 oz. coffees at a major franchised coffee houses often exceed 400 mg (McCusker, Goldberger, & Cone, 2003).

Tasks demanding the executive control of visual attention involve a number of prefrontal brain areas in concert with the anterior cingulate cortex (Botvinick et al., 2001; Bush et al., 1998, 2000; Casey et al., 2000; Fan et al., 2003; MacDonald et al., 2000). These same brain areas have been shown to be up-regulated by caffeine (e.g., Koppelstaetter et al., 2008), and dopamine has been identified as a critical neurotransmitter for supporting executive function in these areas (e.g., Ko et al., 2009). The present findings support the role of caffeine in enhancing conflict resolution through the interaction of dopaminergic pathways with anterior cingulate and prefrontal brain regions. It seems likely that advantages in executive control are only reliably seen with relatively high doses of caffeine in individuals with low-consumption profiles. These effects may be specific to reactive rather than active inhibition (i.e., Fillmore & Rush, 2002); whereas there is some converging evidence that reactive inhibition may be improved as a result of caffeine consumption (see also Hasenfratz & Battig, 1992; Kenemans et al., 1999; Lorist et al., 1994, 1996), no studies examining active inhibition have found such effects (e.g, on stop-signal tasks; Tieges et al., 2009).

Conclusions

Caffeine is an exceedingly common stimulant with diverse influences on central nervous system function. The present study assessed the effects of caffeine on both lower- and higher-level visual attention processes by using the attention network test. We found that caffeine improves participants' ability to efficiently use alerting cues and inhibit the influence of action-incompatible information. The former result is in accordance with several decades of research

demonstrating that caffeine improves performance on tasks requiring sustained attention and vigilance (Fine et al., 1994; Kenemans & Lorist, 1995; Lieberman et al., 2002; Wesensten et al., 2005). The latter result supports some of the extant literature demonstrating beneficial effects of caffeine on executive control in general (Tieges et al., 2006, 2007) and visual selective attention in particular (e.g., Lorist et al., 1994, 1996). This finding, however, contradicts other research demonstrating no effect of caffeine on visual selective attention (Kenemans & Verbaten, 1998; Tieges et al., 2009).

There are few ways to reconcile these differences. Unlike previous studies, participants in the present study were not habitual caffeine consumers and thus may require lower doses to exhibit effects on the executive control of attention. Indeed 200 mg was sufficient to induce performance improvement during conflict resolution, and 400 mg did not improve this process beyond that effect. Such asymptotic effects of caffeine (i.e., Lieberman et al., 1987; Robelin & Rogers, 1998) on higher-order control processes have also been found when using 3 and 6 mg/kg caffeine (Tieges et al., 2006, 2007). It could be the case that reaching asymptotic performance improvements occurs at lower doses in participants with lower consumption profiles. As such, some previous work may not have used a sufficiently high dose (3 mg/kg, Kenemans & Verbaten, 1998; Tieges et al., 2009; 250 mg, Kenemans et al., 1999) to elicit effects amongst habitual consumers[1]. Dose-response manipulations make it possible to examine such possibilities in a range of consumption profiles; we suggest that future research examining caffeine effects on executive control of attention use similar designs.

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[1] In the present study, the low-consumer participants averaged 150lbs in body weight, which approximates a 200 mg dose at 3 mg/kg.

Given the prevalence of caffeine consumption it is critical to understand its effects on the brain and associated cognitive processes. Our results add to a growing body of evidence showing that caffeine can have beneficial effects on attentional processes recruiting brain regions with dense dopaminergic innervation, such as the anterior cingulate cortex, thalamus, and prefrontal cortex (i.e., Coull et al., 1996; Fan et al., 2005; Ferré et al., 1997; Fredholm et al., 1997; García-Cabezas et al., 2007; Hasenfratz & Battig, 1992; Kenemans et al., 1999; Koppelstaetter et al., 2008; Lorist et al., 1994, 1996; Sánchez-González et al., 2005; Sawaguchi & Goldman-Rakic, 1991, 1994; Smits et al., 1987; Tieges et al., 2006; Williams & Goldman-Rakic, 1995).

Table 1. *BMIS adjective ratings as a function of Treatment dosage.*

	Treatment							
	0 mg		100 mg		200 mg		400 mg	
Adjective	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Lively $^{++}$	2.33	.72	2.57	.87	2.75*	.69	3.00*	.83
Happy ^{ns}	2.72	.70	2.78	.86	2.86	.87	2.78	.94
Sad ^{ns}	1.89	.67	1.72	.78	1.67	.72	1.78	.80
Tired ^{m}	2.94	.71	2.72	.85	2.67	.79	2.50	.74
Caring ^{ns}	2.78	.68	2.72	.81	2.64	.80	2.58	.91
Content ^{ns}	2.94	.71	2.97	.74	2.86	.83	2.75	.81
Gloomy ^{ns}	1.58	.65	1.53	.65	1.72	.74	1.61	.69
Jittery $^{++}$	1.69	.62	1.72	.81	2.08*	.94	2.52*	1.05
Drowsy $^{++}$	2.61	.87	2.28	.88	2.53	.88	2.06*	.75
Grouchy ^{ns}	1.78	.83	1.67	.68	1.67	.79	1.67	.72
Peppy $^{++}$	1.83	.74	2.06	.89	2.19*	.92	2.25*	.77
Nervous ^{ns}	1.92	.81	1.78	.68	1.89	.89	1.97	.94
Calm $^{+}$	2.94	.71	2.97	.65	2.69	.79	2.56	.97
Loving ^{ns}	2.61	.80	2.72	.70	2.53	.88	2.47	.88
Fed Up ^{ns}	1.92	.81	1.72	.70	1.75	.77	1.78	.76
Active ^{ns}	2.28	.85	2.61	.87	2.39	.90	2.52	.84

$^{+}$ = $p < .05$; $^{++}$ = $p < .01$; *m* = $p < .10$; *ns* = non-significant in ANOVA.
* = Significant Bonferroni-corrected (α = .017) t-test, comparing treatment level to 0mg placebo.

Figure Caption

Figure 1. Mean difference scores and standard errors for each of the three attention networks and four Treatment levels. Note that higher difference scores in the alerting and orienting networks indicate greater performance; conversely, lower difference scores in the executive control network indicate greater performance.

Author Note

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